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EXAMINER	
ANGELL, JON E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/916,017	Applicant(s) DEBENEDETTI ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All ☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claims 1-18 are pending in the application.

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 10-18) and of the species 5' untranslated sequence of fibroblast growth factor-2 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the product, a DNA vector that constitutively expresses a toxin that is only translated at high levels in cells that express high levels of eIF4E (i.e. tumor cells) would not be useful for any other purpose other than killing the cell in which it is translated.

This is not found persuasive because the breadth of the claims is broad and encompasses any toxin, including conditional toxins (see claim 13). A DNA sequence with the properties mentioned and encoding a conditional toxin could be expressed in a cancer cell without killing the cell. Therefore, the DNA sequence could be used in other materially different processes such as expressing the conditional toxin in a cancer cell. The conditional toxin could be then be purified and used in many different types of experiments such as antibody production. Alternatively, the DNA could be used to express the conditional toxin in a cancer cell in vitro to study the effects different compounds have on the conditional toxin.

Applicants also argue that there is no serious search burden as the class and subclass of the Groups were the same.

However, not only does the search for the DNA sequence require a search of class 514 subclass 44, but also a search of class 536 subclass 23.1 and class 435 subclass 320.1. The classification of Groups into different class and subclass is prima facie evidence of a serious

search burden. Furthermore, evidence that a search of for the DNA sequence does not encompass the search for the method of treatment, the references cited in the 102(b) and 103(a) rejections below clearly anticipated the claimed DNA sequence, but does not anticipate a treatment using the DNA sequence.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a genus of untranslated sequences that inhibit translation in absence of eIF4E and allow translation in the presence of eIF4E. This large genus is represented in the specification only by the disclosure that the sequence is "a relatively long palindromic oligonucleotide sequence that is self-complementary" (see p. 7, first paragraph; and p. 23. first paragraph). Thus, applicants have only disclosed a vague description of a structure characteristic of a genus comprising millions of different possibilities considering the vast

number of sequences, which meet the description "relatively long palindromic oligonucleotide sequence that is self-complementary".

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, a description of the required function of the sequences is disclosed (the ability to inhibit translation in the absence of eIF4E and to allow translation the presence of eIF4E). However, there is no specific description of the structure of any species (i.e. a nucleic acid sequence) of the genus. The only guidance for the identification of sequences that meet the functional limitations is the disclosure that the sequence is "a relatively long palindromic oligonucleotide sequence that is self-complementary".

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, there is only a vague description of a nucleic acid sequence that would inhibit translation in the absence of eIF4E and allow translation in the presence of eIF4E.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or disclosure demonstrating conception or written description of any nucleic acid sequence that has the ability to inhibit translation in the absence of eIF4E and allow translation in the presence if eIF4E.

5. Claims 10-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although the claims are drawn to a product (a DNA sequence), the intended use of the product as set forth in the claims is for "administering to animal to inhibit metastatic tumors" (see claim 10). Therefore the claims broadly encompass gene therapy.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a DNA sequence for administering to a mammal to inhibit one or more metastatic tumors. Therefore the claims encompass the use of a DNA sequence for therapeutic purposes (i.e. gene therapy). Specifically, the claims encompass a type

of gene therapy known as gene directed enzyme prodrug therapy (GDEPT). GDEPT is well known in the art. In general, GDEPT is a two-stage process involving step 1: the administration of a vector encoding a foreign enzyme (e.g. TK) that is selectively expressed in tumor cells, followed by step 2: delivery of a prodrug (e.g. GCV) which is convert into an active (i.e. toxic) form by the enzyme of step 1.

Methods using a GDEPT system utilizing TK/GCV for the treatment of solid tumors were well known in the art at the time of filing (see Kirn et al. Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002). The known systems utilize tumor-specific promoters to confer tumor-specific expression of TK, which selectively express TK in the tumor cells. The instant invention utilizes a similar system; however, rather than using a tumor-specific promoter to regulate the expression of TK, the applicants have used an element that regulates the expression of a toxin (such as TK) at the translational level. Specifically, the instant invention involves a DNA sequence that comprises a constitutive promoter that expresses an mRNA comprising a UTR that confers tumor-specific translation/expression of a toxin. The UTR allows the translation of the toxin in the presence of eIF4E (polypeptide involved in initiating translation) and inhibits translation in the absence of eIF4E. EIF4E is present at low concentrations in wild-type cells and elevated in tumor cells.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass a DNA sequence that when transcribed produces an mRNA comprising a UTR. The UTR can be any sequence having a relatively long palindromic oligonucleotide sequence that is self-complementary—as these are the only structural characteristics disclosed in the specification.

The UTR can be operably linked to any type of toxin. Furthermore, the claims encompass the treatment of any type of metastatic tumor in any animal species, including humans.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples (see page 409, first col.). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

Specifically regarding the efficacy of GDEPT therapy, Beck et al. (Human Gene Therapy, Vol. 6:1525-1530; 1995) teaches that (1) different tumor cell lines vary considerably in their sensitivity to TK/GCV suicide therapy; (2) the concentration of GCV and time needed to eliminate tumor cells varied considerably between different tumor cell lines; (3) ESB-TK tumors were "completely resistant" to TK/GCV therapy; and (4) the different sensitivity was not due to

differences in TK expression levels (see abstract; p. 1527, last paragraph; and Fig. 3). Kirn et al. also points out that "Several advantages [of GDEPT] can be defined: enhanced selectivity of toward cancer cells, amplification effects, and bystander cell death. However, technical hurdles related to the delivery of the foreign gene by viral or non-viral vectors remain to be overcome before reaching therapeutic success. Thus the main requirement for the future is efficient targeting and delivery." (see p. S72 under Concluding Remarks).

Furthermore, the results indicated in the working examples were obtained in tissue culture and in mice, not in human subjects. Crystal (1995) points out that, "predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (see pg 409, col. 1-2). Therefore, results obtained in culture and in mice cannot be extrapolated to humans with a reasonable expectation of success.

Working Examples and Guidance in the Specification

The specification discloses working examples that the claimed DNA sequence (i.e. UTK) can be administered to mouse mammary cells in vitro (both wild-type and tumorigenic cells) resulting in an increased cytotoxic effect on tumorigenic cells compared to the controls when GCV is administered (see Table 2, p. 12). Similar effects are seen in human breast cells in vitro (see Example 4, p. 12). However, consistent with the teaching in the prior art that TK/GCV treatment on different tumor cell types is unpredictability (see Beck et al.), MDA-231 cells were insensitive to treatment (see p. 13, last paragraph). The specification also discloses by example that the DNA sequence (i.e. UTK) can be administered to tumor cells in mice (in vivo) by direct

administration and by systemic administration, resulting in a tumor-specific toxic effect compared to the controls (see Examples 5 and 6, p.14-18).

However, the working examples compare effectiveness of the claimed DNA sequence (i.e. UTK) to a control DNA sequence that constitutively expresses the toxin (TK) in all cell types. It was known in the art that tumor-specific expression of the toxin was critical for effective therapeutic treatment (see above). The GDEPT systems known in the art utilized tumor-specific promoters to confer tumor-specific expression of TK. However, this type of system is still plagued by unpredictable and unreliable results (see above). In order to overcome the unpredictability of tumor treatment using a GDEPT system recognized in the art, the specification would have to show examples that the instant invention overcomes the recognized obstacles and shortcomings. To do this the working examples would have to show that regulating the expression of the toxin (TK) at the translational level overcomes the art recognized problems regarding the use of tumor-specific promoter for regulating toxin expression. However, the working examples only show comparisons of a construct that confers translationally controlled tumor-specific toxin expression to a construct that confers constitutive toxin expression. There are no working examples comparing a construct that confers translationally controlled tumor-specific toxin expression to a construct that confers transcriptionally controlled tumor-specific toxin expression using a tumor-specific promoter. Therefore, there are no working examples showing that the claimed invention overcomes the unpredictability recognized in the art.

Furthermore, there are no working examples using toxins other than HTK. There are now working examples of treatment either in vitro or in vivo of any cell types other than mouse

mammary cells or human breast cells. There are no working examples of treatment in any other species of animal other than mouse. Finally, the only working example of a UTR that can control the translation/expression of the toxin in the presence/absence of eIF4E is the 5' UTR of FGF-2.

Quantity of Experimentation

T he art recognizes that a high level of experimentation is required for the development of a viable and efficacious GDEPT cancer therapy. For example, Kirn et al. (Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002) teaches that the progression of suicide gene therapy approaches to the clinic will require further investigations into effective tumor targeting and vector delivery (see p. S70, second paragraph). Also, Workman et al. (Trends in Mol. Ned. Vol. 8, Suppl: p. S1-S9; 2002) teaches, "The development of optimal schedules and drug combinations requires particularly careful attention so that the therapeutic potential of novel approaches can be fully explored and realized." (See p. S9, third paragraph); and "Even after regulatory approval, it can still take several years of clinical experience to define the optimal role for a new active drug in human cancer." (See p. S9, fourth paragraph).

The quantity of experimentation to determine the reliability and efficacy of the proposed GDEPT system is very large. For example, experimentation is required to test the different toxins encompassed by the invention. Also, the different UTRs encompassed by the claims would have to be tested for their ability to control translation/expression in the presence/absence of eIF4E. Furthermore, experimentation is required to test efficacy of treatment in different

types of tumors. Finally, experiments are required to test the efficacy of the treatment in humans.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 10-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the phrase, "for administering to a mammal to inhibiting one or more metastatic tumors". This phrase renders the claim vague and indefinite because it is unclear what "to inhibiting" means. Amending this claim to recite, "to inhibit" would be clearer. Furthermore, it is unclear what exactly the DNA sequence is inhibiting. For example, the claims could be interpreted to mean that metastatic tumor growth is inhibited, or that metastasis of the

tumor(s) is inhibited. Claims 11-17 are dependent claims which incorporate the same indefinite language and are, therefore, rejected for the same reasons.

8. Claims 11 and 15 recite the limitation "untranslated region" in line 1. There is insufficient antecedent basis for this limitation in the claims as the dependent claim (claim 10) does not recite "untranslated region" but rather "untranslated sequence".

9. Claim 18 is indefinite because it recites the phrase, "A DNA sequence as recited in claim 1". The instant claim appears to be drawn to the DNA sequence (a product); however, claim 1 is a drawn to a process of using the product. Therefore it is unclear of claim 18 is drawn to a product or a process of using the product. For examination purposes, the claim is treated as an independent claim drawn to the DNA sequence.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 10-18 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by DeFatta (Dissertation, catalogued and placed on the shelf March 20, 2001).

DeFatta teaches a DNA sequence comprising a constitutive promoter operably linked to a transcription sequence, when transcribed produces a mRNA sequence that comprises a translatable sequence encoding herpes Thymidine Kinase (HTK) (a conditional toxin) and an

untranslated sequence comprising an untranslated sequence with a stability of $\Delta G \geq 50$ Kcal/Mol (see p.95, second paragraph), such as the 5'untranslated sequence of FGF-2 (see p. 47, second paragraph); wherein the untranslated sequence inhibits translation of the toxin in the absence of eIF4E and wherein the untranslated sequence allows translation of HTK the presence of eIF4E (see p. 92-95 and Fig. 2).

12. Claims 10, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimogori et al. (BBRC Vol. 223:544-548; 1996).

Shimogori et al. teaches a DNA sequence comprising a constitutive promoter operably linked to a transcription sequence that when transcribed, produces a mRNA comprising a translatable sequence encoding the conditional toxin Thymidine Kinase (TK) and an untranslated sequence (for e.g. see abstract; p. 545, last two paragraphs; and "Construction of plasmids" under Materials and Methods). Given the description of the untranslated sequence in the specification simply as "a relatively long palindromic oligonucleotide sequence that is self-complementary" (see p. 7, first paragraph; and p. 23. first paragraph) that the DNA sequence taught by Shimogori et al. inherently comprises a GC rich untranslated sequence which has all of the structural characteristics of the DNA sequence described in the specification.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims rejected under 35 U.S.C. 103(a) as being unpatentable over Strathdee et al. (BioTechniques Vol. 28:210-214; 2000) and in view of Kevil et al. (Oncogene Vol. 11:2339-2348).

Strathdee et al. teaches a system for studying the activity of gene regulatory regions using a vector/vectors comprising a constitutive promoter operably linked to multiple selectable marker genes wherein one of the selectable marker genes is TK (a negative selection marker) (see p. 210, first column and Fig. 1.) for the purpose of studying the function of genetic regulatory regions. For instance, Strathdee et al. teaches, "The vectors are well suited to serve as qualitative and quantitative probes of promoter or enhancer strength." (see p. 212, last paragraph).

Strathdee et al. does not teach that the vector comprises the selectable marker under control of the regulatory activity of the FGF-2 untranslated sequence.

Kevil et al. teaches that the 5'-untranslated sequence of FGF-2 mRNA has regulatory effects on the translation/expression of FGF-2 polypeptide. Specifically, Kevil et al. teaches that the FGF-2 mRNA of most mammals contains a ~500 nt long G+C-rich 5' UTR, with potential for forming extensive secondary structure that would be strongly inhibitory to translation (see p. 2340, second paragraph). Kevil et al. also teaches that the regulatory region of the FGF-2 5' UTR can be cloned into an expression vector to confer regulation of translation/expression (see FIG. 1; FIG 2; and p. 2341, second column).

Kevil et al. does not teach that the FGF-2 5' UTR can be can be operatively linked in a vector to the gene encoding TK.

However, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of Strathdee et al. and Kevil et al. to make a vector comprising a constitutive promoter that expresses a mRNA comprising the 5' UTR of FGF-2 operably linked to TK.

The motivation to combine the references would have been to further study the regulatory functions of the 5' UTR of FGF-2 taught by Kevil et al. by operably linking it to the selectable marker gene TK, in a vector as taught by Strathdee et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
April 19, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER